REMARKS

Claims 22, 24-29, 31-34, and 36-38 are pending. Claims 22, and 31-34 have been amended to clarify the methods of the invention, such that the claimed methods are drawn to the inhibition of HBV replication. Support for the amendments is found throughout the application as filed. For example, at page 17, line 31 to page 18, line 14; page 31, lines 1 to 5; page 53, lines 16 to 29; and page 57, lines 16 to 23.

Applicants believe that the amendments do not introduce new matter. Accordingly, Applicants respectfully request entry of the amendments and remarks made herein into the file history of the present application. Upon entry of the present amendments, claims 22, 24-34 and 36-38 will be pending and under consideration.

The Rejections Under 35 U.S.C. § 112, First Paragraph Should Be Withdrawn

The Examiner rejected claims 22, 24-29, 31-34, and 36-38 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to allow one skilled in the relevant art to which it pertains to make and/or use the invention commensurate in scope with the claims.

Specifically, the Examiner has maintained the rejection of these claims as set forth in the prior Office Action, dated December 7, 2004. However, the Examiner has apparently retreated from his earlier position that Applicants' specification is enabling only with respect to the *in vitro* methods described in the specification, and not with respect to an *in vivo* method for treating patients infected with hepatitis B virus (HBV) by administering a compound that modulates cytosolic calcium as determined by an *in vitro* assay (see Office Action page 3, lines 4-5 of item 4). The Examiner now maintains that Applicants' specification does not provide any *in vitro* evidence to support the ability of each of the species of calcium inhibitors listed in claims 28, 32, 33, and 38, to inhibit HBV infection.

In response, without agreeing with the Examiner in any manner and merely to clarify the instant invention and advance prosecution, Applicants have amended claim 22 (on which claim 28 ultimately depends), and claims 32-34 such that the claimed methods are drawn to the inhibition of HBV replication. However, because claim 36 is also drawn to inhibition of HBV replication and the Examiner has rejected claim 38 (which depends on claim 36), Applicants assume that the Examiner's rejection is based on an alleged lack enablement for the use of any calcium inhibitor, with the exception of cyclosporine. Applicants point out that under the applicable case law, it is improper to limit Applicants to the specific example

presented, notwithstanding the disclosure and enablement of a broader invention. See In re Anderson, 176 U.S.P.Q. 331, 333 (C.C.P.A. 1973); In re Kamal, 158 U.S.P.Q. 320, 323 (C.C.P.A. 1968).

The test for enablement is whether one reasonably skilled in the art could make or use the invention, without undue experimentation, from the disclosure in the patent specification coupled with information known in the art at the time the patent application was filed. U.S. v. Telectronics Inc., 857 F.2d 778, 8 U.S.P.Q.2d 1217 (Fed. Cir. 1988). One skilled in the art is presumed to use the information available to him in attempting to make or use the claimed invention. See Northern Telecom, Inc. v. Datapoint Corp., 908 F.2d 931, 941 (Fed. Cir. 1990) ("A decision on the issue of enablement requires determination of whether a person skilled in the pertinent art, using the knowledge available to such a person and the disclosure in the patent document, could make and use the invention without undue experimentation."). These enablement rules preclude the need for the patent applicant to "set forth every minute detail regarding the invention." Phillips Petroleum Co. v. United States Steel Corp., 673 F. Supp. 1278, 1291 (D. Del. 1991); see also DeGeorge v. Bernier, 768 F.2d 1318, 1323 (Fed. Cir. 1985).

Undue experimentation is experimentation that would require a level of ingenuity beyond what is expected from one of ordinary skill in the field. Fields v. Conover, 170 USPQ 276, 279 (CCPA 1971). The factors that can be considered in determining whether an amount of experimentation is undue have been listed in In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Among these factors are: the amount of effort involved, the guidance provided by the specification, the presence of working examples, the amount of pertinent literature and the level of skill in the art. The test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, so long as it is merely routine. *Id.*

Applicants respectfully point out that enabling support for the claimed methods is provided throughout the specification in form of guidance on how to identify a compound which modulates HBV replication using *in vitro* or *in vivo* methods. Applicants direct the Examiner's attention to the detailed description of *in vitro* assays that may be used to evaluate HBV replication in response to test compounds at page 49, line 14 to page 54, line 18 of the specification. Applicants additionally point to the working examples demonstrating the use of *in vitro* assays to identify compounds that modulate cytosolic calcium and inhibit HBV replication (see the specification, Example 12, at pages 79 to 83).

Methods for estimating the therapeutically effective dose of such identified compounds from *in vitro* results (see the specification page 45, lines 1-14 and the Office Action, page 3, lines 4-5 of item 4) are well known in the art. Given the detailed teachings in the specification as described above, the amount of literature referred to in the specification, and the high level of skill in the art, the experimentation to make and use the claimed methods throughout their scope is routine and thus, the full scope of the claimed methods is enabled.

As argued in the previous response, the Examiner has not come forward with any specific evidence to substantiate the speculative assertion that some of the claimed calcium inhibitors may not inhibit HBV replication. The Patent and Trademark Office bears the initial burden of establishing a prima facie case of non-enablement. In re Marzocchi, 169 USPQ 367, 369 (C.C.P.A. 1971); MPEP § 2164.02. A patent applicant's specification which contains a teaching of how to make and use the invention must be taken as enabling unless there is reason to doubt the objective truth of the teachings which must be relied on for enabling support. Id. Applicants point out that it is taught by the specification that HBV replication requires the presence of cytoplasmic calcium. Treatment of HBV infected cells with an inhibitor of cytosolic calcium release, cyclosporin A, or a chelator of cytosolic calcium, BAPTA-AM (which, in effect, renders cytoplasmic calcium unavailable), was shown to significantly impair HBV replication relative to untreated controls (see the specification at page 82, lines 9 to 23). Compounds that inhibit cytosolic calcium release and methods of their use are well known in the art (see, *e.g.*, the specification at page 26, line 30 to page 27, line 27). Applicants have provided working examples demonstrating the inhibition of HBV replication in an *in vitro* assay using exemplary modulators of cytosolic calcium, *e.g.*, an inhibitor of cytosolic calcium release. Applicants submit that only routine experimentation by a skilled person is required to practice the claimed invention. If the Examiner is relying on any other facts within his personal knowledge as to why the methods of the invention would not be effective in inhibiting HBV replication he is hereby requested to supply an affidavit specifying with particularity the support for the rejection. 37 C.F.R. § 1.104(d)(2).

In view of the foregoing, Applicants respectfully request withdrawal of the rejection.

The Rejection Under 35 U.S.C. § 102(b) Should Be Withdrawn

The Examiner rejected claims 22, 24-29, 31-33, and 36 under 35 U.S.C. § 102(b) as allegedly anticipated by Friedrich et al. (Z. Gastroenerol. 1988 26:265-270, hereinafter "Friedrich"). Specifically, the Examiner asserted that Friedrich teaches each of

the steps of the claimed methods directed to treating HBV by administering a compound that inhibits cytosolic calcium release.

In response, Applicants respectfully traverse the Examiner's rejection and submit that Friedrich fails to teach or fairly suggest each and every element of the claims as amended.

The legal standard for anticipation under 35 U.S.C. § 102 (b) is one of strict identity. A claim is anticipated only if each and every element set forth in the claim is found, either expressly or inherently, in a single prior art reference. *Verdegaal Bros., Inc. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051 (Fed. Cir. 1987); *Schering Corp. v. Geneva Pharmaceuticals, Inc.*, 339 F.3d 1373, 1377, 67 U.S.P.Q.2d 1664 (Fed. Cir. 2003); and *Atlas Powder Co. v. IRECO, Inc.*,190 F.3d 1342, 1347, 51 U.S.P.Q.2d 1943 (Fed. Cir. 1999). In other words, there must be no difference between the claimed invention and the reference disclosure as viewed by a person of ordinary skill in the field of the invention. *Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565, 1576, 18 U.S.P.Q.2d 1896 (Fed. Cir. 1991). See also, *Richardson v. Suzuki Motor Co., Ltd.*, 868 F.2d 1226, 1236, 9 U.S.P.Q.2d 1913 (Fed. Cir. 1989; "...identical invention must be shown in as complete detail as is contained in the patent claim").

In response to the Examiner's rejection, Applicants submit that Friedrich fails to teach or fairly suggest the inhibition of HBV replication by the administration of cyclosporin to an HBV infected patient. For example, at page 268, col. 1, second full paragraph, Friedrich teaches that the only patient with chronic Hepatitis B that showed any improvements following administration of cyclosporin A, did not demonstrate any improvement or modification of the levels of HBV markers such as HBs-Ag, HBe-Ag, anti-HBc-IgM, and HBV-bound DNA polymerase. The lack of change in the level of HBV markers is indicative of no inhibition of HBV viral replication, leading Friedrich to conclude that cyclosporin does not influence HBV viral activity (see page 269, Col. 2, first paragraph of the Conclusion). Therefore, as Friedrich fails to describe, much less teach, the inhibition of viral replication by administration of cyclosporin, Friedrich cannot anticipate the claimed invention and fails to anticipate the claims under 35 U.S.C. § 102 (b).

In summary, Applicants submit that Friedrich fails to anticipate any of claims 22, 24-29, 31-33, and 36, and respectfully request that the Examiner withdraw his rejection of these claims under 35 U.S.C. § 102(b).

The Objection Under 35 U.S.C. § 112, first paragraph (New Matter), Should Be Withdrawn

The Examiner objected to claim 37 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner alleged that the specification as filed does not support the step of measuring the viral proteins selected from the group consisting of HBcAg, HBsAg, and the polymerase protein, as recited in claim 37.

In response, Applicants maintain that claim 37 is support by Applicants' disclosure as originally filed. The specification specifically teaches that viral proteins may be measured as a means of determining the levels of viral replication. For example, at page 56, lines 2-9, the specification teaches that, "levels of HBV replication in the presence or absence of test compounds may also be determined by measuring levels of extracellular virus which is released or intracellular viral transcripts and/or viral proteins, including the surface antigen and the polymerase protein..." HBcAg and HBsAg are specifically taught by the specification to be viral proteins, in particular, components of the viral particle detectable by ELISA (see the specification at page 53, line 29, "[t]he level of [HBV] particle [sic] secreted into the medium can be assayed using commercial ELISA kits to detect the presence of HBV/WHV HBcAg and HBsAg.") Because they are taught to be quantitative markers of HBV/WHV particles that are detectable by ELISA, one of skill in the art would immediately recognize that HBcAg and HBsAg are proteins specifically associated with HBV/WHV, *i.e.*, viral proteins. The specification therefore teaches that HBcAg and HBsAg are viral proteins and that such proteins are markers of HBV replication. Thus, the method of claim 37 is not new matter and the rejection under 35 U.S.C. § 112, first paragraph, should be withdrawn.

CONCLUSION

Applicants respectfully request that the amendments and remarks made herein be entered and made of record in the file history of the present application. Withdrawal of the Examiner's rejections and a notice of allowance are earnestly requested.

If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

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Date: January 17, 2006

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